



## Vaccine

journal homepage: [www.elsevier.com/locate/vaccine](http://www.elsevier.com/locate/vaccine)Deaths averted by influenza vaccination in the U.S. during the seasons 2005/06 through 2013/14<sup>☆</sup>Ivo M. Foppa<sup>a,b,\*</sup>, Po-Yung Cheng<sup>a,b</sup>, Sue B. Reynolds<sup>a,c</sup>, David K. Shay<sup>a</sup>, Cristina Carias<sup>d,e</sup>, Joseph S. Bresee<sup>a</sup>, Inkyu K. Kim<sup>a,b</sup>, Manoj Gambhir<sup>d</sup>, Alicia M. Fry<sup>a</sup><sup>a</sup> Influenza Division, Centers for Disease Control and Prevention, 1600 Clifton Road NE, MS A-20, Atlanta, 30333 GA, USA<sup>b</sup> Battelle Memorial Institute, Atlanta, GA, USA<sup>c</sup> Atlanta Research and Education Foundation, GA, USA<sup>d</sup> National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA<sup>e</sup> IHRC, Inc, Atlanta, GA, USA

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## ABSTRACT

**Background:** Excess mortality due to seasonal influenza is substantial, yet quantitative estimates of the benefit of annual vaccination programs on influenza-associated mortality are lacking.**Methods:** We estimated the numbers of deaths averted by vaccination in four age groups (0.5 to 4, 5 to 19, 20 to 64 and  $\geq 65$  yrs.) for the nine influenza seasons from 2005/6 through 2013/14. These estimates were obtained using a Monte Carlo approach applied to weekly U.S. age group-specific estimates of influenza-associated excess mortality, monthly vaccination coverage estimates and summary seasonal influenza vaccine effectiveness estimates to obtain estimates of the number of deaths averted by vaccination. The estimates are conservative as they do not include indirect vaccination effects.**Results:** From August, 2005 through June, 2014, we estimated that 40,127 (95% confidence interval [CI] 25,694 to 59,210) deaths were averted by influenza vaccination. We found that of all studied seasons the most deaths were averted by influenza vaccination during the 2012/13 season (9398; 95% CI 2,386 to 19,897) and the fewest during the 2009/10 pandemic (222; 95% CI 79 to 347). Of all influenza-associated deaths averted, 88.9% (95% CI 83 to 92.5%) were in people  $\geq 65$  yrs. old.**Conclusions:** The estimated number of deaths averted by the US annual influenza vaccination program is considerable, especially among elderly adults and even when vaccine effectiveness is modest, such as in the 2012/13 season. As indirect effects ("herd immunity") of vaccination are ignored, these estimates represent lower bound estimates and are thus conservative given valid excess mortality estimates© 2015 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## 1. Introduction

In the U.S., seasonal influenza has been estimated to be associated with an average of ~25,000 [1,2] to 35,000 [3] annual deaths. In 1960, annual influenza vaccination was recommended in the U.S. for persons aged  $\geq 65$  yrs., for those with chronic debilitating disease as well as for pregnant women [4]. Influenza vaccination recommendations were broadened over time until 2010, when annual influenza vaccination was recommended for all people  $\geq 6$  months of age [5]. Recently, Kostova et al. [6] found a substantial benefit of the current influenza vaccination program in the United

States on the total number of influenza cases and hospitalizations, based on data on laboratory-confirmed influenza-associated hospitalizations. Similar estimates of mortality averted by vaccination would further help prioritize public health interventions and facilitate communications regarding the need and value of influenza prevention. We sought to estimate the number of deaths averted by annual influenza vaccination in the United States from the influenza seasons 2005/06 through 2013/14. Our aim is to provide conservative seasonal and age group-specific estimates for the number of deaths averted by the US influenza vaccination program.

## 2. Methods

## 2.1. Averted deaths formula

The number of deaths averted by influenza vaccination  $d_A$  was estimated by multiplying the number of deaths expected in the

<sup>☆</sup> The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

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**Table 1**

Vaccine effectiveness estimates by study type, season and age range with their respective literature references.

Season	Age range (yrs.)	Study type	VE (95% CI)	Reference
2005/06	≥0.5	TND <sup>a</sup>	21 (–52, 59) <sup>b</sup>	[10]
2005/06	18–48	RCT <sup>c</sup>	16 (–171, 70)	[11]
2005/06	≥5	TND	61 (26, 79)	[12]
2006/07	≥0.5	TND	52 (22, 70)	[10]
2006/07	≥9	TND	46 (17, 65)	[13]
2007/08	18–49	RCT	68 (46, 81)	[14]
2007/08	0.5–4	TND	39 (2, 62)	[15]
2007/08	≥0.5	TND	37 (22, 49)	[15]
2007/08	≥0.5	TND	60 (45, 71)	[16]
2008/09	≥0.5	TND	56 (41, 67)	[17]
2009/10	≥0.5	TND	56 (23, 75) <sup>d</sup>	[18]
2010/11	0.5–4	TND	67 (53, 77)	[19]
2010/11	5–19	TND	59 (45, 70)	[19]
2010/11	20–64	TND	50 (36, 62)	[19]
2010/11	≥65	TND	36 (–22, 66)	[19]
2011/12	0.5–4	TND	49 (12, 70)	[20]
2011/12	5–19	TND	50 (29, 65)	[20]
2011/12	20–64	TND	46 (28, 59)	[20]
2011/12	≥65	TND	43 (–18, 72)	[20]
2012/13	0.5–4	TND	58 (40, 71)	[21]
2012/13	5–19	TND	46 (32, 57)	[21]
2012/13	20–64	TND	52 (43, 60)	[21]
2012/13	≥65	TND	32 (0, 56)	[21]
2013/14	0.5–4	TND	47 (14, 67)	[22]
2013/14	5–19	TND	56 (37, 69)	[22]
2013/14	20–64	TND	52 (42, 61)	[22]
2013/14	≥65	TND	39 (0, 65)	[22]

<sup>a</sup> Case test-negative design (see, e.g., [7]).

<sup>b</sup> Point estimate (95% confidence interval).

<sup>c</sup> Randomized controlled trial.

<sup>d</sup> Effectiveness of monovalent pandemic vaccine.

absence of vaccination ( $D$ ) by the proportion effectively vaccinated, i.e.:

$$d_A = D \times v\phi \quad (1)$$

where,  $v$  denotes vaccination coverage (seasonal influenza vaccine) and  $\phi$  denotes vaccine effectiveness (VE) of the seasonal influenza vaccine. The number of excess deaths in the absence of vaccination is calculated by dividing the number of excess deaths due to influenza under the current vaccination program ( $\varepsilon$ ) by the proportion not protected by vaccination ( $1 - v\phi$ ), i.e.:

$$D = \frac{\varepsilon}{1 - v\phi}. \quad (2)$$

Note that all quantities are indexed by time. For instance,  $d_A$  may refer to the deaths averted in a given month.

## 2.2. Data

### 2.2.1. Vaccine effectiveness (VE)

We used published estimates of VE against acute respiratory illness (ARI) due to any laboratory-confirmed influenza virus infection for the influenza seasons (Northern Hemisphere) 2005/6, through 2013/14 which were derived from either case test-negative control studies [7–9] or from randomized controlled trials, conducted in outpatient settings in North American populations. We used estimates that were from subjects of a broad age range (e.g. 6 months or older or 18–48 yrs.) or were restricted to one of our age groups (e.g. ≥65 yrs.) [10–22] (Table 1). Up to 2010/11 we mostly used the same estimates Kostova et al. [6] used for their analysis of cases and hospitalizations averted by influenza vaccination; however, we excluded one unpublished study (see reference 11 in [6]) and one study that included non-North American populations [23], added one study that had been published since [16] as well as three studies estimating VE for the three recent influenza seasons (2011/12, 2012/13 and 2013/14, respectively) [20,24,25].

**Table 2**

Empirical distributions of vaccine effectiveness by season and age group as they were used for the calculation of averted deaths.

Season	0.5–4 yrs	5–19 yrs	20–64 yrs	≥65 yrs
2005/06	44 (3,77) <sup>a</sup>	44 (3,77)	44 (3,77)	29 (2,65)
2006/07	49 (19,68)	49 (19,68)	49 (19,68)	32 (12,58)
2007/08	39 (8,62) <sup>b</sup>	42 (24,74)	42 (24,74)	29 (13,61)
2008/09	56 (42,67)	56 (42,67)	56 (42,67)	39 (22,59)
2009/10	56 (21,74)	56 (21,74)	56 (21,74)	36 (13,65)
2010/11	67 (52,77) <sup>b</sup>	59 (46,70) <sup>b</sup>	50 (35,61) <sup>b</sup>	37 (5,67) <sup>b</sup>
2011/12	49 (15,71) <sup>b</sup>	50 (30,65) <sup>b</sup>	45 (30,58) <sup>b</sup>	45 (7,74) <sup>b</sup>
2012/13	58 (40,70) <sup>b</sup>	46 (33,58) <sup>b</sup>	52 (43,60) <sup>b</sup>	31 (5,56) <sup>b</sup>
2013/14	47 (17,67) <sup>b</sup>	56 (37,69) <sup>b</sup>	52 (41,60) <sup>b</sup>	40 (7,64) <sup>b</sup>

<sup>a</sup> Point estimate in percentage (95% confidence interval).

<sup>b</sup> Based on age group-specific estimate.

VE is believed to decline with increasing age above ~65 yrs. [26], but there are few published estimates of VE among those 65 yrs. old, particularly for specific seasons. If, for a particular season, no age group-specific estimates were available for persons aged ≥65 yrs. (e.g. prior to 2008/9), we assumed, in concordance with [6], the VE of that age group to be 0.7 of the VE reported for the younger age group on average (uniform distribution in the range 40%–100% to reflect uncertainty). The assumption of an average attenuation of 30% is also compatible with observations for the seasons when VE estimates for persons <65 yrs. old and ≥65 yrs. old were available (2010/11, 2011/12 and 2012/13). In those years, the average relative VE for those ≥65 yrs. old ( $VE_{\geq 65}/VE_{<65}$ ; iteratively calculated from draws from sampling distributions) was 73% (95% CI 10% to 176%). Table 2 displays the empirical distributions of annual age group-specific VEs.

### 2.2.2. Vaccination coverage (VC)

Monthly VC estimates by age group were obtained from the National Health Immunization Survey (NHIS) (Dr. P Lu, CDC, personal communication). Coverage was assumed constant over a month. For the months of June and July for which no coverage estimates are available, zero coverage was assumed. To account for a two-week delay in the development of effective immunity after vaccination, we assumed that the effective coverage in a given month was the average between last month's and current month's coverage. For the season 2013/14, for which no data were available at the time of this analysis, the same monthly coverage was assumed as in 2012/13 season. Vaccination coverage increased over the study period, especially in subjects under 65 yrs. of age, but there was little change between 2011/12 and 2012/13. For example, estimated coverage, in the age group 6 months to 4 yrs., was 42.7% (95% CI 39.8%, 45.8%) and 42.6% (39.8%, 45.6%) in November, respectively, and 62.4% (58.9%, 65.9%) and 63.5% (60.0%, 67.1%), in May of the following year, respectively. The assumption of unchanged coverage thus tends to understate the number of deaths averted.

### 2.2.3. Mortality data

To estimate the weekly number of deaths attributable to influenza by age group we used weekly age group-specific (0.5 to 4 yrs., 5 to 19 yrs., 20 to 64 yrs., 65+ yrs.) mortality data from the National Center for Health Statistics (NCHS) for 2005 through 2012. Deaths were categorized using the International Classification of Diseases, 10th Revision (ICD-10) codes. For the purposes of estimating deaths potentially averted by the influenza vaccination program, we focused on underlying causes of death categorized as respiratory and circulatory (R&C) in nature, corresponding to ICD-10 codes I00–I99 and J00–J99. For each mortality record, a single underlying cause is listed, defined as “the disease or injury which initiated the train of morbid events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury”, in accordance with the rules of the International

**Table 3**

Estimated numbers of excess deaths due to influenza (all ages) for the seasons 2005/6 through 2012/13 (August through July of the following year).

Season	6 months–4 yrs	5–19 yrs	20–64 yrs	≥65 yrs	All
2005/6	21 (12,34) <sup>a</sup>	26 (16,40)	1483 (1122,1848)	9185 (7545,10774)	10714 (9015,12363)
2006/7	65 (41,92)	82 (56,110)	1442 (1019,1925)	9002 (6671,11367)	10612 (8226,13003)
2007/8	76 (51,104)	93 (66,122)	3297 (2672,3934)	18916 (15932,22043)	22385 (19246,25567)
2008/9	92 (58,131)	114 (78,151)	1844 (1250,2523)	10209 (7056,13288)	12275 (9041,15445)
2009/10	110 (63,165)	276 (217,339)	5293 (4279,6356)	3939 (2694,6107)	9656 (7967,12047)
2010/11	60 (36,89)	89 (63,119)	4049 (3341,4757)	17492 (14682,20363)	21680 (18693,24711)
2011/12	28 (16,43)	40 (27,56)	2048 (1692,2421)	10019 (8402,11717)	12151 (10467,13880)
2012/13	84 (43,133)	99 (55,152)	6084 (4920,7384)	30822 (25891,35924)	37102 (31868,42422)
2013/14	51 (32,80)	105 (80,156)	2594 (2063,3375)	4718 (3668,6176)	7505 (6260,9140)
All seasons	592 (428,772)	929 (749,1130)	28148 (24161,32437)	114346 (97171,132006)	144109 (125586,161988)

<sup>a</sup> Median of posterior distribution (95% credible interval).

Classification of Diseases [27]. For the time period for which the NCHS data was not yet available (January, 2013 through July, 2014) we assumed the same relationship between influenza incidence and mortality as for the preceding time period.

#### 2.2.4. Influenza indicator

To construct an indicator of influenza-associated mortality, we used weekly proportion of respiratory samples testing positive for specific types (A,B) and subtypes (A(H1N1), A(2009 H1N1), A(H3N2)) of influenza from the U.S. World Health Organization (WHO) Collaborating Laboratories and the National Respiratory and Enteric Virus Surveillance System (NREVSS) [28] from the eight seasons, 2005/6 through 2013/14. The number of specific influenza A subtypes was augmented by adding the product of the weekly proportion of a specific subtype in the subtyped influenza A specimens and the number of unsubtyped or unsubtypable influenza A viruses. These proportions were multiplied by the number of influenza-like illness (ILI) visits per reporting provider in the U.S. Outpatient ILI Surveillance Network (ILINet) [28]. This influenza indicator is derived in Supplement S2.

#### 2.3. Excess mortality estimation

We estimated U.S. excess mortality due to influenza using a statistical approach structurally similar to one previously described [2], for the period of the first epidemiological week of October of 2005 through the last week of July, 2014. Briefly, we modeled the weekly age group-specific R&C mortality (ICD-10 codes I00–I99, J00–J99) as a gamma-Poisson mixture [30] (negative Binomial) distribution with the Poisson parameter being a function of seasonally periodic variations, influenza incidence indicators (Supplement S2) and temporal trends to accommodate both demographic changes, as well as changes in the surveillance process and/or the virulence of the circulating influenza types/subtypes. The model is described in detail in Supplement S1. The model was fit using Markov chain Monte Carlo (MCMC) algorithms as implemented in JAGS [31] and interfaced with R [29] by the R-package rjags [32]. For most model parameters we assumed flat Normal priors centered at 0, with variance 1.0E6, but truncated at zero, except for the parameters driving the sinusoidal baseline mortality (see Supplement S1). For the size parameters of the negative Binomial distributions, uniform priors were assumed (range 0 to 1.0E6). Three thousand samples were obtained by selecting each fifth sample of 5000 iterations in three chains, resulting in 3000 samples for each parameter, after a burn-in period of 20,000 iterations.

The weekly excess mortality for each age group was directly obtained from the model coefficients (see Supplement S1) and was summed over seasons. Following Kostova et al. [6] we only considered the weeks from October through April for most seasons except for the 2009/10 pandemic, when we used the months from May (2008) through April (2010), as well as for the seasons 2011/2012

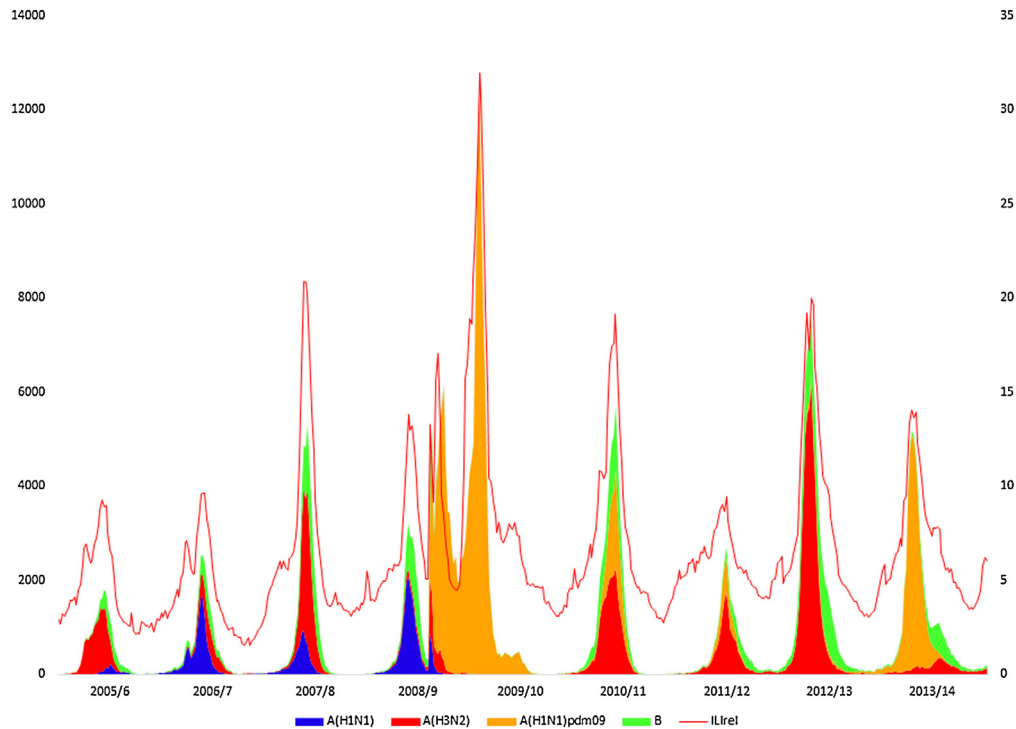
(October, 2011 through September, 2012) and 2013/14 (October, 2013 through July, 2014). The construction of Monte Carlo confidence intervals is described in Supplement S5.

### 3. Results

During the study period, the highest numbers of deaths associated with influenza occurred during the season 2012/13, followed by 2007/8 and 2010/11 (Table 3). Each of these three seasons were dominated by circulation of influenza A(H3N2) and influenza B viruses (Fig. 1). There were relatively few influenza-associated excess deaths in the 2006/7, 2008/9, 2009/10 and 2013/14 seasons, when influenza A(H1N1) and influenza B viruses predominated (Figs. 1 and 2, Table 3).

The number of deaths averted each season by vaccination depended linearly on the number of excess deaths as well as on the odds of being effectively vaccinated,  $\frac{v\phi}{1-v\phi}$  (see Eq. (1) and (2)). To the extent that VE as well as vaccination coverage vary by season, numbers of deaths potentially averted by vaccination would be therefore expected to be more variable than the number of estimated excess deaths attributed to influenza (Table 4). This becomes particularly evident when comparing the 2009/10 A(H1N1)pdm09 pandemic, when an estimated 9656 (95% CI 7967 to 12,047) deaths were estimated to be associated with influenza, with the 2012/13 season when close to 40,000 deaths, nearly four times as many, were attributed to influenza (Table 3). However, more than forty times more deaths were estimated to be averted during the 2012/13 compared to the 2009/10 season (Table 4). This apparent discrepancy was largely due to the timing of vaccination: the monovalent vaccine against pandemic influenza A(H1N1)pdm09 became available in the United States on a broad basis only at the tail end of the 2009/10 pandemic while in 2012/13, like in most seasons, vaccination uptake is concentrated before the bulk of the seasonal epidemic. Over the nine seasons included in this study, we estimated that over forty thousand deaths were averted by the US influenza vaccination program (Table 4). Almost ninety percent of the deaths averted (88.9%; 95% CI 83 to 92.5%, not shown) would have occurred, in the absence of vaccination, in those ≥65 yrs. old.

Over the whole study period, we estimated that the influenza mortality prevented by the vaccination program (i.e., the averted fraction) was a little less than a fourth (Table 5). The overall averted fraction was highest in the oldest age group, driven by high vaccination coverage, followed by the youngest age group. The fraction averted in the intermediate age categories was substantially lower (Table 5). In all age groups the averted fraction was substantially higher at the end than the beginning of the study period (Table 5). During the 2013/14 season in persons aged ≥65 yrs., over a fourth of the influenza deaths expected in the absence of vaccination were averted by vaccination. By contrast, during the 2009/10 pandemic, when mortality rates were reduced in that age group, only about one percent of the deaths were averted by vaccination, but the



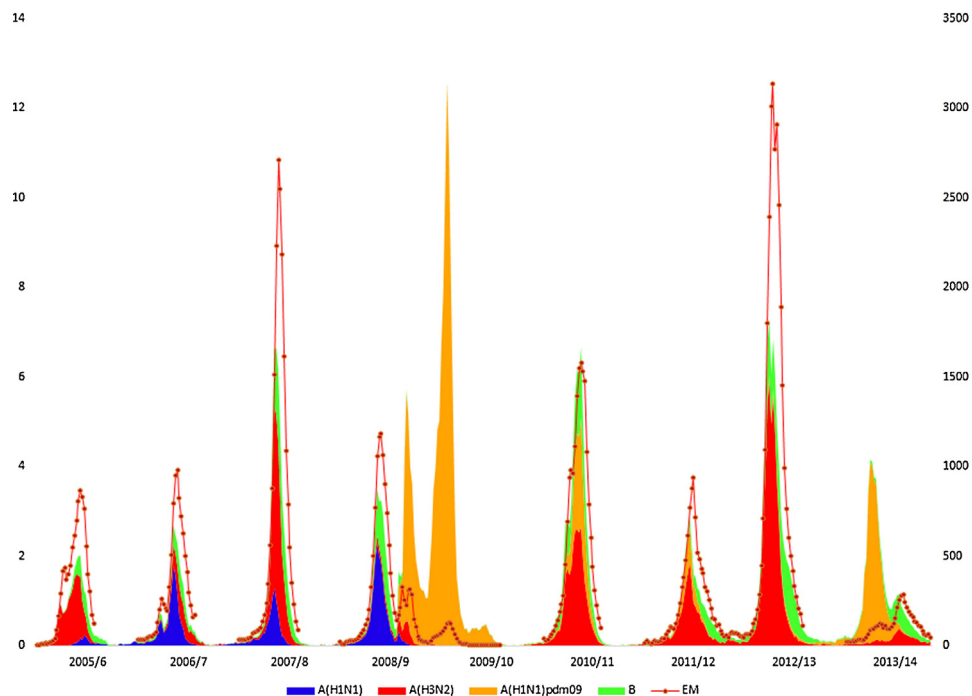
**Fig. 1.** The number of influenza-like illness (ILI) visits reported by provider (ILI relative) and the number of specimens testing positive for influenza A(H1N1), A(H3N2), A(H1N1) pdm09 and B viruses, October, 2005 through July, 2014.

proportion averted was almost seven percent in the youngest age group.

#### 4. Discussion

We estimated that annual influenza vaccination averted almost a fourth of predicted influenza-associated deaths during the nine seasons 2005/6 through 2013/14. Almost 90% of the averted deaths

would have occurred among persons aged  $\geq 65$  yrs. Mortality due to seasonal influenza is substantial, especially among elderly adults [2,3,33–46]. Kostova et al. [6] also found the predominance of averted hospitalizations from influenza vaccination in those  $\geq 65$  yrs. old. The estimated numbers of deaths averted by vaccination varied by season with most deaths estimated to be averted during 2012/13 and the fewest deaths averted during 2009/10. Using very different methods and data, Borse et al. [47] also found that



**Fig. 2.** The median number of deaths associated with influenza (excess mortality=EM) and the indicators for influenza A(H1N1), A(H3N2), A(H1N1) pdm09 and B viruses, October, 2005 through July, 2014.



**Table 4**

The estimated number of deaths averted by influenza vaccination from August, 2005 through July, 2013, by influenza season and age group.

Season	6 months–4 yrs	5–19 yrs	20–64 yrs	≥65 yrs	All
2005/6	4 (0.9) <sup>a</sup>	2 (0.4)	143 (11,292)	2094 (141,6872)	2250 (151,7138)
2006/7	16 (5.30)	8 (3.14)	174 (63,293)	2406 (712,5782)	2606 (806,6085)
2007/8	16 (2.32)	10 (4.20)	409 (194,799)	4647 (1715,13689)	5112 (1965,14393)
2008/9	34 (19.55)	20 (13.29)	339 (209,509)	3575 (1574,7338)	3983 (1920,7787)
2009/10	8 (2.15)	14 (5.21)	153 (56,229)	43 (9,124)	222 (79,347)
2010/11	34 (18.55)	24 (15.35)	709 (456,971)	5915 (598,14091)	6692 (1406,15019)
2011/12	12 (2.25)	10 (5.15)	351 (210,511)	4456 (364,10865)	4821 (811,11250)
2012/13	37 (17.69)	21 (10.36)	1253 (909,1663)	8088 (989,18528)	9398 (2386,19897)
2013/14	18 (5.37)	29 (17.47)	559 (386,778)	1799 (210,4054)	2412 (847,4662)
All seasons	182 (122,258)	139 (103,183)	4144 (3298,5141)	35563 (21337,54505)	40127 (25694,59210)

<sup>a</sup> Median number averted (95% empirical confidence interval).

numbers of deaths averted by vaccination during the 2009/10 influenza A(H1N1) pandemic, when the pandemic vaccine was not widely available until well after the peak of influenza infections had occurred, were low. Their estimate of 305 deaths averted was remarkably similar to ours (222).

The differences in the averted death estimates by season were related to the inter-seasonal differences in influenza-associated excess mortality and vaccine effectiveness estimates. The substantial inter-seasonal variability in influenza-associated excess mortality has been attributed to differences in the intensity of seasonal influenza epidemics [48], virulence of seasonally predominant circulating influenza viruses [44,49] and population-based levels of immunity [44]. The factors that influence seasonal differences in vaccine effectiveness are complex, but are related in part to antigenic similarities between circulating and vaccine viruses.

Ecological studies, using non-specific outcomes, have cast doubt on the effectiveness of influenza vaccine to avert deaths in adults ≥65 yrs. of age [39,50]. Clinical trial data for that age group are scarce and suggest an efficacy below 50% [51]. This is also true for estimates from observational studies for the influenza seasons 2010/11 [19], 2011/12 [20], 2012/13 [21] and 2013/14 [22]. Yet, even with our conservative method, we estimated a substantial number of deaths averted by vaccination in this age group, even during years with lower vaccine effectiveness estimates for elderly adults compared to younger adults.

Our findings should be interpreted in light of several limitations. First and most importantly, we did not consider the indirect effects of influenza vaccination programs [52]. An important consequence of an indirect effect is the existence of a critical vaccination coverage threshold (i.e.  $\nu\phi$ ) above which transmission of the targeted agent is disrupted [53]. If a population is vaccinated above that threshold, then excess mortality due to that agent would tend to zero and, in that situation, all deaths would have been averted. However, Eq. (1) suggests that, when influenza transmission is

effectively disrupted resulting in the absence of excess mortality, the calculated number of deaths averted would be zero. Such finding clearly would be incorrect since, in fact, *all* deaths would have been averted. This contradiction arises because Eq. (1) requires a 100% effective coverage (coverage times effectiveness =  $\nu\phi$ ) level to completely eliminate infection-related deaths, whereas elimination can actually be achieved below 100% effective coverage if herd immunity is accounted for. Furthermore, if influenza mortality in a particular season was low because of vaccination, a low excess mortality and thus averted deaths estimate would result. By focusing only on direct effects, our estimates of averted deaths therefore are conservative (see also Supplement S4). While the degree of underestimation will need to be quantified, especially for a more accurate valuation of influenza vaccination, our estimates are substantial enough to support the need for annual influenza vaccination campaigns.

Second, our estimates of the number of deaths averted by vaccination are driven by excess deaths estimates which were obtained by an “ecological” (as opposed to individual-based) study design. These kinds of analyses are prone to confounding [54]. Even though we were unable to directly adjust for confounding we sought to improve the validity of our excess mortality estimates by using a novel influenza incidence indicator which is similar to the indicator proposed by Goldstein et al. [55], rather than using only the proportion of tests “positive” for influenza. The resulting excess mortality estimates were, in fact, proportional to laboratory-confirmed influenza hospitalizations [6] (data not shown), suggesting good validity. Still, over-estimation of influenza associated excess mortality remains a possibility.

Third, we assumed that the relationship between influenza type and subtype-specific incidence and mortality was similar for the period from 2005 through 2012, for which we had complete NCHS mortality data and the period from January 2013 through July 2014, for which we lacked data. It is possible, although

**Table 5**

The estimated proportion (in percent) of deaths averted by influenza vaccination from August, 2005 through July, 2013, by influenza season and age group.

Season	6 months–4 yrs	5–19 yrs	20–64 yrs	65+ yrs	All
2005/6	15.2 (0.9,26.6) <sup>a</sup>	6.5 (0.4,11.3)	8.8 (0.5,15.3)	18.9 (0.9,42.5)	17.9 (0.8,39.6)
2006/7	20.3 (8.1,28.1)	9.3 (3.8,12.9)	11.1 (4.5,15.2)	21.1 (8.1,37.6)	19.8 (7.8,35)
2007/8	17.4 (3.6,28.1)	9.3 (5.1,16.4)	10.9 (5.9,19.1)	19.6 (8.6,41.5)	18.5 (8.4,38.7)
2008/9	27.5 (20.5,33)	15.3 (11.4,18.2)	15.8 (11.8,18.6)	26.3 (14.9,40.2)	24.6 (14.8,37.4)
2009/10	6.9 (2.5,9.8)	4.8 (1.8,6.6)	2.8 (1.1,3.9)	1.1 (0.3,2.4)	2.3 (0.8,3.2)
2010/11	36.4 (28.1,42.3)	21.8 (16.8,25.9)	15 (10.4,18.7)	26.5 (3.4,45.6)	24.6 (6.41.7)
2011/12	29.6 (8.6,43.3)	19.6 (11.3,25)	14.7 (9.4,18.8)	32 (5.4,51.4)	29.5 (7.1,47.4)
2012/13	31.3 (21.6,38.3)	17.5 (12.6,22.1)	17.2 (14.2,19.8)	21 (3,37.2)	20.4 (5.8,34.6)
2013/14	26.2 (8.6,37.8)	21.6 (14.4,27)	17.9 (14.1,21)	28 (4.8,45.1)	24.5 (10,37.7)
All seasons	23.5 (19.8,27)	13 (11.2,14.8)	12.8 (11.2,14.4)	24 (16.4,32.1)	22 (15.6,29)

<sup>a</sup> Median (95% empirical confidence interval).

unlikely, that this relationship change which would have biased our results.

Fourth, most vaccine effectiveness estimates were based on studies with an outcome of laboratory confirmed influenza associated ambulatory care visits for acute respiratory infection. Vaccine effectiveness estimates for more severe outcomes, such as hospitalization, with laboratory-confirmed influenza are limited and vaccine effectiveness estimates for laboratory-confirmed influenza associated deaths are lacking entirely. However, several published studies suggest that the vaccine effectiveness estimates from studies with laboratory confirmed influenza associated hospitalization outcomes are similar to or higher [56–58] than the estimates used in our model. We did not use these studies because they either were conducted among non-North American populations [58] or because of the fact that the case test-negative design has not yet been validated for hospitalization outcomes [56,57]. To the extent that the VE estimates used in our analysis were invalid, the estimated averted fraction will be biased as was shown for hospitalizations averted by vaccination [59]. In our own sensitivity analysis for the age group  $\geq 65$  yrs. we found that, even under most adverse conditions (VE = 10%) in a moderately severe seasons such as 2012/13 substantial numbers of deaths can be averted by the influenza vaccination program (2,129; 95% CI 1785 to 2481) (see Supplement S6).

Finally, as an infectious phenomenon, influenza incidence is spatially heterogeneous [60] and vaccination coverage may vary substantially by region [61]. Our analysis, however, ignored any spatial heterogeneity in inputs and modeled outcomes. Averted deaths may thus be underestimated, even in the absence of bias. For the sake of the argument, assume that in a specific geographic region, vaccination against influenza is above a critical threshold level, such that influenza transmission is disrupted. Consequently, the true excess mortality due to influenza in that geographic region would be close to zero, contributing little to overall excess mortality and resulting in a “diluted” averted deaths estimate.

## 5. Conclusions

We estimated that a substantial number and proportion of influenza-related deaths were averted by recent U.S. influenza vaccination campaigns, even when indirect benefits of vaccination were not considered. Our findings support annual influenza vaccination in the United States and suggest that both increased vaccination coverage and increased vaccine effectiveness would result in even more deaths averted.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.vaccine.2015.02.042>.

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